Economic and Epidemiological Impact of Dengue in Brazil (2000-2015) from a public health system perspective: Implications of adopting of a dengue vaccine

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Abstract

Introduction: Dengue is a serious global health problem endemic in Brazil. Consequently, our aim was to measure the costs and disease burden of symptomatic dengue infections in Brazil from the perspective of the Brazilian Public Health System (SUS) between 2000 and 2015 using Brazilian public health system databases. Specific age group incidence estimates were used to calculate the disability-adjusted life years (DALYs) to gain a better understanding of the disease burden. Areas covered: SUS spent almost USD159 million and USD10 million to treat dengue and severe dengue, respectively, between 2000-2015. This is principally hospitalization costs with the majority of patients self-treated at home with minor symptoms. The average notification rate for dengue was 273 per 100,000 inhabitants and 3 per 100,000 for severe dengue, with annual DALYs estimates ranging between 72.35 to 6,824.45 during the 16 years. Expert commentary: The epidemiological and morbidity burden associated with dengue is substantial in Brazil, with costs affected by the fact that most patients self-treat at home with these costs not included in SUS. The Brazilian government urgently needs to proactively evaluate the real costs and clinical benefits of any potential dengue vaccination program by the National Immunization Program to guide future decision making.

Keywords: Burden of Disease, Epidemiology, Economic, Dengue, Public Health, Brazil

1. Introduction

Dengue virus (DENV) is a serious threat to public health, with an estimated of 3.97 billion people at risk worldwide [1,2]. It is caused by four distinct strains of *Flavivirus* (DENV1-4) and is transmitted by mosquitos of the *Aedes* genus. The global estimates of the prevalence of dengue vary with approximately 50 to 200 million dengue infections annually, with 500,000 cases of severe dengue and over 20,000 deaths annually [3,4]. As a result, DENV is currently considered the most important vector-borne infection in several endemic countries. Most of the at-risk population live in tropical and subtropical regions, where conditions are favorable for mosquitos with the Americas, South-East Asia, and the Western Pacific regions the most seriously affected [5-12].

Dengue is a major public health problem in Brazil and is endemic in all regions of the country, with mandatory notification to the Brazilian Notifiable Diseases Information System (SINAN). SINAN was started in 1990, and the system was introduced countrywide in 1994 to collect and process individual notification forms and the follow-up of cases (three levels: municipality, state and federal government) [13-16]. According to SINAN, approximately 9.5 million dengue cases were notified between 2000 and 2015 in Brazil, with the number of notified cases increasing from approximately 696,000 in 2002 to 1.68 million cases in 2015 [17-19]. Recognizing the challenges of dengue, the Brazilian Ministry of Health developed the National Dengue Control Program in early 2002 with its main objectives being the reduction of infestation by *Aedes aegypti*, the incidence of dengue, and deaths due to severe cases [20].

The majority of individuals with dengue in Brazil self-treat at home because the symptoms usually last between two and seven days and are not severe enough to access SUS services [21]. However, some patients can develop severe symptoms that necessitate hospitalization services. These include leukopenia (reduction in white blood cells, hemorrhage (bleeding) and circulatory collapse (shock) associated with deaths [22]. Currently, there is no specific antiviral treatment to manage the dengue virus [23-26]. At the end of 2015, the Brazilian Government approved the first dengue vaccine (CYD-TDV; Dengvaxia®) to prevent DENV infection with a reported global efficacy of 60%, recommended for individuals between 9 and 45 years old [27,28].

Several studies have estimated the economic [4,29-34] and disease burden of dengue in endemic countries including Brazil [35-38]. However, economic analyses of the impact of dengue in Brazil have included only a few cities, e.g. Goiania, Belo Horizonte, Rio de Janeiro, Teresina, Recife and Belem [34], or a low number of individuals (n=550) [29]. Moreover, these publications did not include all the available dengue registers that are currently used in the Brazilian Public Health System (Sistema Único de Saúde - SUS) services. i.e. the Hospitalization Information System (SIH/SUS). Within SUS, healthcare services including medicines are provided free of charge to patients who meet the agreed criteria. We believe it is essential to include these data alongside assessing disease burden through measures such as disability-adjusted life years (DALYs) to fully understand the economic and disease burden of dengue in Brazil, as recommended by Brazilian Ministry of Health [39, 40]. DALYs are typically used to measure the burden of disease and have been verified to evaluate the burden of dengue in endemic countries [41, 42]. They are a composite measure of years of life lost (YLL) and the years lived with disability (YLD) [41], and represent one lost year of "healthy" life. The sum of DALYs for a disease can measure the gap between the current health status and an ideal health situation [43].

Researching issues of the current economic and disease burden of dengue within a public healthcare system is a crucial first step before assessing the potential role and value of new health technologies to prevent or treat the disease. This includes funding decisions for new vaccines alongside funding existing prevention programmes. We have already undertaken a willingness to pay study for the dengue vaccine in Brazil, and we believe this analysis will add to this information when the authorities in Brazil and other countries assess new technologies for dengue [9].

Consequently, the objective of this study is to measure the costs and disease burden of symptomatic DENV infections in Brazil from the SUS (national health) perspective. We believe this is the first study

to fully evaluate the hospitalization and other SUS services involved in Brazil considering the reported frequency and costs with this arbovirus based on all the dengue registers over the past 16 years.

As a result, we believe this comprehensive approach can contribute to future discussions on the development of public policies to control dengue infection in Brazil and other endemic countries. This includes deliberations regarding the funding of new treatment approaches at requested prices.

2. Patients and Methods

2.1 Study Design and Population

We conducted a descriptive study involved different Brazilian Health Databases to demonstrate the epidemiological, morbidity and economic impact of dengue in an important endemic country. Brazil is a tropical country, localized in the South America with more than 200 million inhabitants, and has 26 states and the Federal District distributed in five regions (North, Northeast, South, Southeast and Midwest). According to the National Survey of Domicile conducted by Brazilian Institute of Geography and Statistics (IBGE), in 2013, the highest share of residents in the country is located in the Southeast region with 42% of the population, followed by the Northeast. 84% of the inhabitants live in urban areas. The mean income per capita was US$315.97 (1128.00BRL) in 2014 [44]. The country's public health system, named SUS, was established in 1988 by a constitutional decree in order to guarantee access to health care to the entire population. SUS maintains primary and outpatient centers, hospitals, diagnostic laboratories and provides access to pharmaceuticals including vaccines. There are a several SUS databases pertaining to different sectors of the health system such as the Ambulatory Information System (SIA/SUS), Hospitalization Information System (SIH/SUS) and Mortality Information System (SIM/SUS) [15, 16, 21].

This study assessed the profile of services and procedures performed for the treatment of dengue and severe dengue throughout Brazil between January 2000 and December 2015 from the SUS perspective, i.e. the public healthcare system perspective. During the study period, it was possible to see that the dengue epidemics, in different years, involved the four serotypes [45]. Our study included all registers associated with dengue and severe dengue in the country obtained from the different SUS databases such as SINAN, SIH/SUS and SIM/SUS yielding, respectively, notification as well as hospitalization cases and deaths (2000-2015). As mentioned, dengue is a mandatory notification disease in Brazil, in other words, all new cases of this infection need to be registered in the SINAN database, which is a specific SUS Database associated with mandatory notification of diseases [16]. However, only the severe cases generally consume hospital services, with the majority of patients undergoing self-treated at home which are not covered by SUS; consequently, the extent of their utilization and costs are not recorded in the SUS databases [22].

The data used were extracted through the deterministic-probabilistic link involving various SUS administrative databases, i.e. the Hospital Information System (SIH) and the Mortality Information System (SIM) [46-49]. The data derived from these systems were used to obtain epidemiological parameters and expenditures with the disease in Brazil. In addition, the Mortality Information System (SIM/SUS) was used to record deaths due to dengue occurring between January 2000 and December 2015.

Until 2014, the common serious dengue manifestation, which has the presence of bleeding and other severe symptoms, was denoted as dengue hemorrhagic fever; thereafter, this was changed to severe dengue. Both denominations were coded with the same ICD: A91. In our study, we collected all registers with ICD-10 A90 and A91 using SUS databases (SIH/SUS) and dates involving dengue hemorrhagic fever (until 2014) and severe dengue (after 2014) to estimate the dengue notification incidence.

It is important to highlight that SINAN (notification), SIH (hospitalization) and SIM (mortality) are completely independent SUS databases. The analyses were conducted using the R Software [50] and Microsoft Excel 2010.

2.2 Profile of dengue cases in Brazil

We estimated the median incidence of dengue for each year based on all registers of notification and hospitalization cases for dengue and severe dengue between 2000 and 2015. Since dengue is an

infection associated with four serotypes an individual can be infected more than one time in the same year, which can result in more than one notification (register applied for a symptomatic case) or hospitalization case (SIH/SUS) for each individual. We considered the number of new cases registered, obtained by SINAN and SIH/SUS in the country divided by the national population, and expressed this per 100 thousand inhabitants to calculate the dengue incidence for each context (notification and hospitalization), in line with information provided by the Ministry of Health [15, 20]. The number of new cases was obtained from the SINAN database [16-19]. The number of new hospitalization cases were obtained from the SIH/SUS database, extracted through the deterministic-probabilistic link. In this scenario, we included all individuals who had dengue (SUS code: 74500457, 74300440, 0303010010) and severe dengue (SUS code: 74300628, 74500627, 0303010029) registered in the SUS databases. We assessed the distribution of dengue and severe dengue cases in Brazil considering the total number of patients on the hospitalization registers in terms of their gender, region and age (in years) groups, involving children, adolescents and adults, which is similar to other studies [43, 51].

The mortality was assessed from the number of deaths associated with ICD-A90 (dengue) and A91 (severe dengue). After this, we evaluated mortality by age, year, and location.

2.3 Costs of treatment

In order to better understand the costs incurred for this infection in the country, all records of procedures performed in the country associated with the treatment of dengue (Procedures: 74300440, 74500457, 0303010010; ICD-10: A90) and severe dengue were analyzed. In addition, all associated procedures (Supplementary Material) presented in Dengue Guidelines of the Ministry of Health [12] as these services for the treatment of dengue are covered by SUS. All death registries were also interrogated in order to better understand the full impact of dengue in Brazil from a SUS perspective. We did not include any costs associated with self-treatment at home as these are not covered by SUS.

All procedures and costs were obtained via the Hospital Information System (SIH) from 2000 until 2015. We included procedures utilized until 90 days after dengue or severe dengue was registered in the SUS database. The list of procedures selected and associated with dengue or severe dengue were included in the Supplementary Material (TS1). These procedures are associated with clinical activities, examinations or complications applied to dengue and severe dengue in accordance with the Dengue Guideline [12]. These costs in the database for dengue and severe dengue were converted to US dollars according to World Bank (2017: USD 1 = 3.191 BRL) for comparative purposes.

2.4 Burden of disease (DALY)

We also estimated the disability-adjusted life years (DALYs) to measure the burden of dengue. We calculated DALY using the equations below, considering the discount rate [42].

$$DALY = YLL + YLD$$

$$YLL = \frac{N}{r}\left(1 - e^{-rL}\right)$$

$$YLD = I\ X\ DW\ X\ L\left(1 - e^{-rL}\right) \div r$$

Where: N = number of deaths; L (YLL) = standard life expectancy at age of death in year; I: number of incident cases; DW = disability weight; r = discount rate; L (YLD)= duration of disability (years).

Since the numbers of hospitalizations represent most of the dengue cases and deaths in Brazil, we assessed the burden using data on hospitalization. We calculated the DALYs for 17 age groups in 5-year increments (<5 years old to >80 years old), similar to a previously published study for comparative purposes [30]. We obtained the number of dengue and severe dengue cases and deaths for each age group from the profile of this infection in Brazil through the Hospitalization Databases (SIH/SUS) per year. We used disability weights of 0.051 and 0.133 for dengue and severe dengue, respectively, in accordance with the Global Burden of Disease Study 2015 [52]. Life expectancy

expectations were taken from World Health Organization life tables [53]. In addition, according to the Ministry of Health in Brazil, the mean duration of hospital stay for dengue and severe dengue in Brazil is currently three and five days, respectively [54].

A discount rate of 5% was used to estimate the burden of disease as indicated by the Brazilian Ministry of Health [39, 40]. The parameters involved in this evaluation were presented in Supplementary Material (Table S3).

2.5 Ethics

This study was approved by the Ethics Committee of Federal University of Minas Gerais (COEP) under the CAAE 57219816.0.0000.5149.

3. Results

3.1 Dengue Profile in Brazil (2000-2015)

A total of 702,270 individuals with dengue, and 29,925 with severe dengue, used SUS services between 2000 and 2015, and 739,177 hospitalization procedures were verified as dengue and severe dengue. Table 1 provides the characteristics of the population associated with dengue and severe dengue in Brazil between 2000 and 2015. The majority of verified cases were among females: 53.69% dengue cases and 52.15% severe dengue cases. Individuals between 5 and 44 years represented 68.04% and 72.14% of dengue and severe dengue cases respectively.

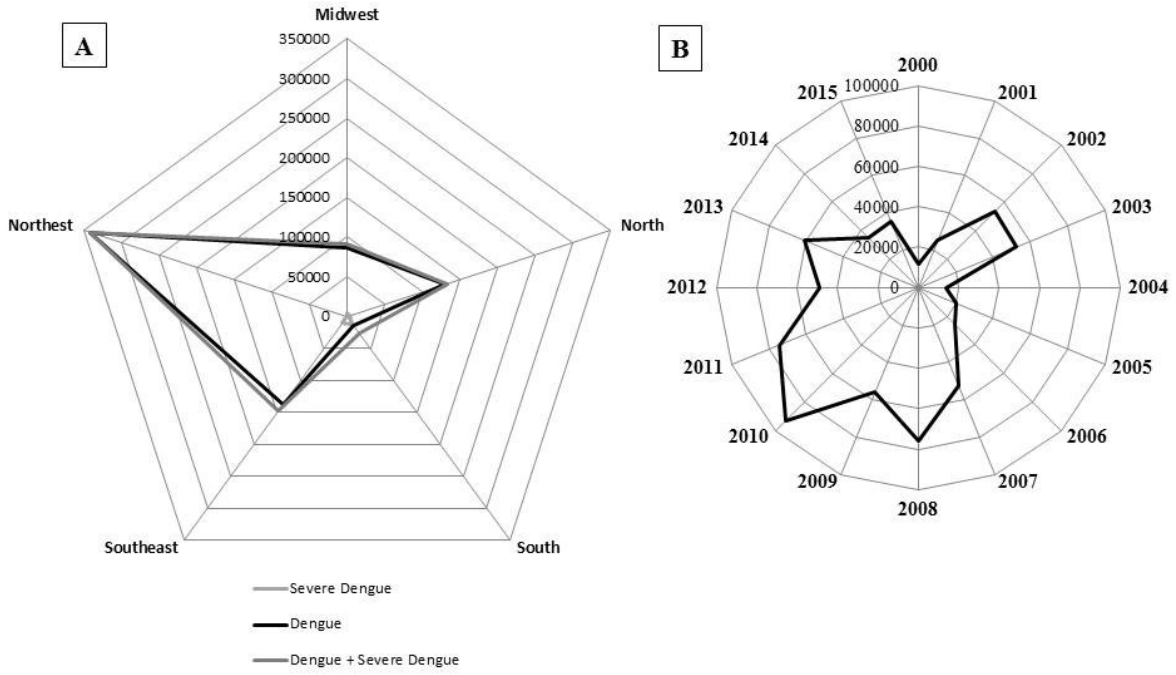
2.3% of individuals had more than one dengue episode in the same year. This was especially common in the Northeast. Reported rates of dengue and severe dengue varied by region, as shown in Figure 1A. The Northeast and Southeast had the highest number of cases; combined, they accounted for over 66% of dengue cases across the country. The South had the lowest number of cases at almost 2% of cases. The highest number of cases occurred in 2002, 2008, 2010, and 2013, when epidemics occurred (Figure 1B).

Table 1: Characteristics of Population: Profile of Dengue and Severe Dengue in Brazil 2000-2015

Variable	Dengue	Severe Dengue
N° individuals (n)	702,270	29,925
Gender (%)		
Men	45.77	47.31
Female	53.69	52.15
NA	0.54	0.54
Frequency per age group (years-old) (%)		
< 1	1.37	2.53
1-4	4.24	5.66
5-14	17.64	31.02
15-24	20.38	15.30
25-34	16.91	14.30
35-44	13.11	11.52
45-54	10.40	8.87
55-64	7.49	5.42
65-74	4.96	3.25
75-84	2.68	1.69
≥ 85	0.82	0.44
Had dengue more than one time in the same year (%)	0.93	1.38

NB: NA = Not available

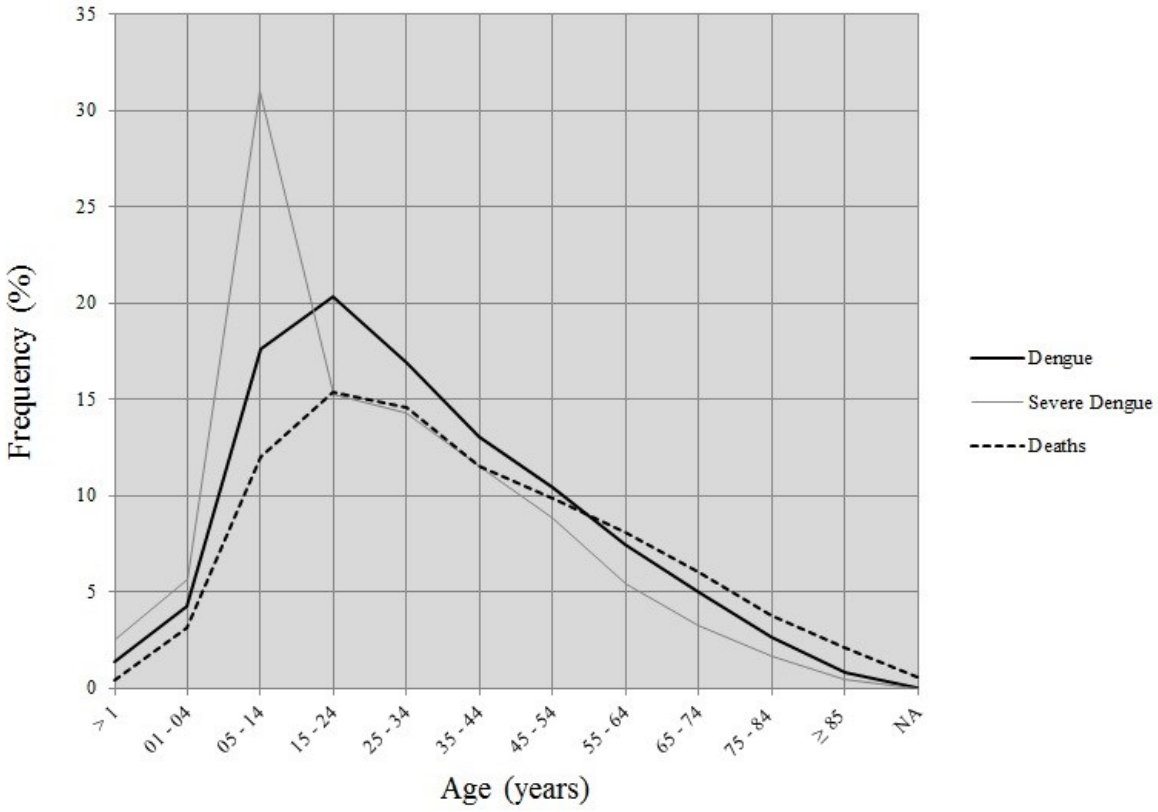
Figure 1: Distribution of Dengue cases by region and year in Brazil (2000-2015)



	Midwest	North	South	Southeast	Northest	Brazil
Severe Dengue	4155	2646	12125	10626	373	29925
Dengue	86931	129977	14324	137034	340534	708800
Dengue + Severe Dengue	91086	132623	26449	147660	340907	738725

Figure 2 shows the dengue disease burden by age group. The highest percentage of cases occurred in age groups 5 to 14 years old (dengue: 17.6% and severe dengue: 31.0%) and 15 to 24 years old (dengue: 20.4% and severe dengue: 15.3%). In other words, the number of dengue cases and deaths were highest among children, adolescents and young adults among the age groups 15 to 24 (dengue cases: 20.38%; death: 15.42%). Adults and elderly people between 45 and 84 years old represented 27.8% of the recorded deaths.

Figure 2: Distribution of Dengue, Severe Dengue and Deaths per age in Brazil



3.2 Dengue and Severe Dengue profile and incidence in Brazil

The number of registered dengue and severe dengue cases, combining ambulatory care and hospitalization, are reported in Table 2. The number of hospitalizations observed between 2000 and 2015 are shown in Figure 3. The median incidence of notifications and hospitalizations were 273 cases/100,000 and 3 cases/100,000 inhabitants respectively. The respective incidence of severe dengue were 25 cases/100,000 inhabitants and 1 case/100,000 inhabitants verified from SUS Hospitalization Information System Database.

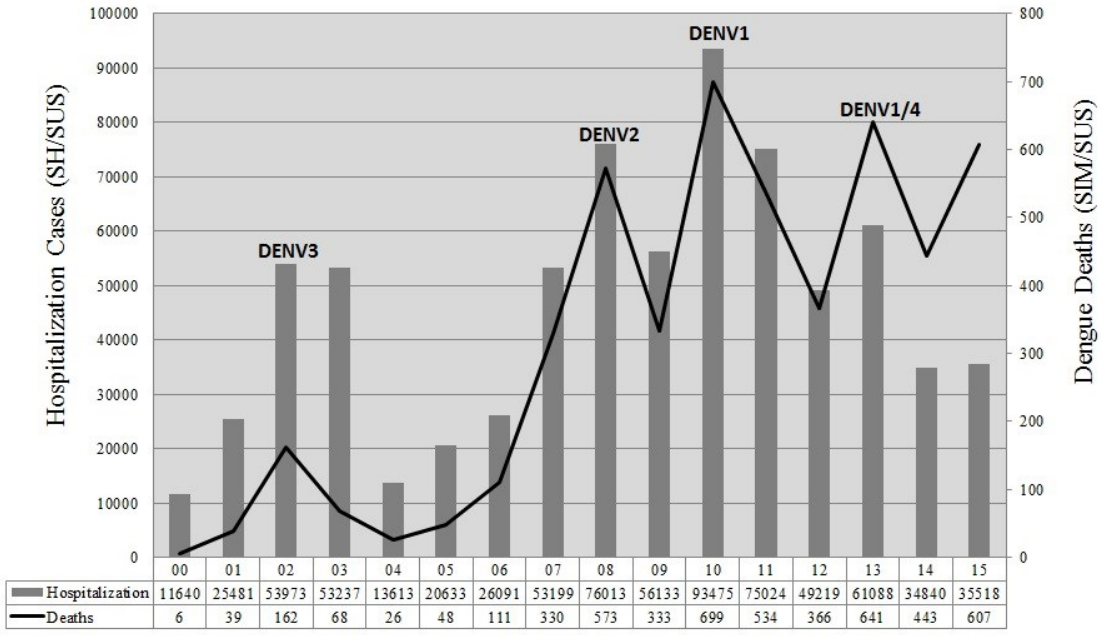
Disease incidence, hospitalizations, and deaths where highest in the years when there was an epidemic, i.e. 2002, 2008, 2010, 2013, as demonstrated in Table 2.

Table 2: Epidemiological burden of dengue and severe dengue in Brazil (2000-2015) by SUS perspective

Year	Inhabitants	Dengue *Notification Cases (SINAN)	Dengue Incidence (/100,000 inhab)	Dengue N° Infected Individuals	Dengue Hospitalization Cases (SIH/SUS)	Dengue Incidence (/100,000 inhab)	Severe Dengue *Notification Cases (SINAN)	Severe Dengue Incidence (/100,000 inhab)	Severe Dengue N° Infected Individuals	Severe Dengue Hospitalization Cases (SIH/SUS)	Severe Dengue Incidence (/100,000 inhab)
2000	173,448,346	134,527	78	11,202	11,637	6.71	701	0	3	3	0.00
2001	175,885,229	384,330	219	24,459	25,322	14.40	1,453	1	155	159	0.09
2002	178,276,128	689,119	387	50,878	52,655	29.54	7,353	4	1,295	1,318	0.74
2003	180,619,108	271,521	150	50,774	52,472	29.05	3,454	2	751	765	0.42
2004	182,911,487	69,394	38	13,042	13,447	7.35	780	0	156	166	0.09
2005	185,150,806	145,194	78	19,750	20,363	11.00	1.845	1	269	270	0.15
2006	187,335,137	255,767	137	24,568	25,371	13.54	2.913	2	697	720	0.38
2007	189,462,755	490,940	259	48,987	50,512	26.66	5.983	3	2,579	2,687	1.42
2008	191,532,439	608,109	317	66,842	69,200	36.13	24.571	13	6,567	6,813	3.56
2009	193,543,969	395,851	205	51,244	53,219	27.50	10.418	5	2,800	2,914	1.51
2010	195,497,797	994,074	508	84,769	87,652	44.84	17.474	9	5,599	5,823	2.98
2011	197,397,018	753,486	382	69,149	71,176	36.06	10.546	5	3,724	3,848	1.95
2012	199.242.464	585,166	294	46,603	47,782	23.98	4.425	2	1,388	1,437	0.72
2013	201,032,714	1,445,634	719	58,293	59,577	29.64	6.855	3	1,459	1,511	0.75
2014	202,768,562	579,921	286	33,093	33,809	16.67	9.186	5	985	1,031	0.51
2015	204,450,649	1,665,819	815	34,104	34,606	16.93	22.869	11	880	912	0.45
Median			**273**			25		**3**			**1**

*SINAN Databases [17, 18]. Note: Dengue is an infectious disease associated with four serotypes (DENV1-4) and Brazil is an endemic country where an individual can be infected more than once, which can result in more than one hospitalization case (SIH/SUS) for each individual.

Figure 3: Hospitalization cases and dengue deaths per year in Brazil (2000-2015)



	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15
Hospitalization	11640	25481	53973	53237	13613	20633	26091	53199	76013	56133	93475	75024	49219	61088	34840	35518
Deaths	6	39	162	68	26	48	111	330	573	333	699	534	366	641	443	607

3.3 Costs of dengue and severe dengue in Brazil

Tables 3 and 4 document the costs of dengue and severe dengue among hospitalized patients from a SUS perspective.

Table 3: Summary of hospitalization costs (USD) and deaths associated with dengue and severe dengue in Brazil and regions (2000-2015)

Region	Dengue Individuals (n)	Dengue Hospitalization (n)	Dengue Costs (USD)	Severe Dengue Individuals (n)	Severe Dengue Hospitalization (n)	Severe Dengue Costs (USD)	Deaths
Brazil	702270	708800	159508032.00	29925	29759	11022610.00	4986
Midwest	86232	86931	18747434.00	4146	4155	1830598.00	671
North	128471	129917	28969052.00	2620	2646	936572.80	878
Northeast	336222	340534	76587483.00	12102	12125	4261169.00	2135
Southeast	137035	137034	32193144.00	10684	10626	3802647.75	1182
South	14310	14324	3010919.00	373	373	191622.45	120

Table 4: Economic Impact (USD) associated with Dengue and Severe Dengue in Brazil by SUS perspective (2000-2015)

Year	Dengue Hospitalization (USD)	per capita	Severe Dengue Hospitalization (USD)	per capita	Total Costs
2000	2729654.25	243.57	861.96	287.32	2730516.21
2001	5688683	232.49	39088.32	252.18	5727771.32
2002	14419091	283.32	446867	345.07	14865958
2003	13066798	257.28	250124.09	333.05	13316922.09
2004	3211473.5	246.18	50957.67	326.65	3262431.17
2005	4704780	238.20	86419.10	321.26	4791199.1
2006	5762687.5	234.49	224385.30	321.93	5987072.8
2007	11507461	234.82	831978.25	322.60	12339439.25
2008	16416964	245.46	1982478	301.88	18399442
2009	13004050	253.66	1187017.50	423.93	14191067.5
2010	20087610	236.82	2070013.12	369.71	22157623.12
2011	15339574	221.45	1237327.12	332.26	16576901.12
2012	9608115	206.02	537325.12	387.12	10145440.12
2013	11437396	196.02	596482.44	408.83	12033878.44
2014	6252689.50	188.70	360707.97	366.20	6613397.47
2015	6073313	177.73	288376.53	327.70	6361689.53

The estimated total global direct medical costs of dengue and severe dengue for the Brazilian public healthcare system (SUS) were USD159.5 million and USD 11.3 million, respectively, during the 16 years (2000-2015). The treatment costs with dengue and severe dengue associated with the Southeast and Northeast represented almost 21.0% (USD76 million) and 48% (USD 32 million) of the total costs across the country during this period, demonstrating differences within the regions of Brazil.

Among the estimated costs, approximately, USD 604,000 was spent on dengue clinical complications (e.g. chronic pulmonary disease, fluid and electrolyte disorders) during the 16 years (2000-2015) (TS2 Supplementary Material). The cost breakdowns are shown in detail in Table 4.

3.4 Burden of disease (DALY)

Table 5 provides estimates of the disease burden by year based on patients accessing SUS services for dengue and severe dengue. The estimated DALYs were highest in epidemic periods, i.e. 2002 (1824.40), 2008 (6625.18), 2010 (6824.45), 2013 (5872.27) and 2015 (4155.96), which results in a higher relative weight of adults compared children.

Table 5: Estimated DALYs by year in Brazil (2000-2015)

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Dengue																
YLLs	37.76	180.11	1001.64	418.62	138.20	237.42	741.89	2446.92	3433.16	2272.62	5338.75	4919.42	2837.74	5578.17	4214.06	6363.33
YDLs	4.88	10.62	22.08	22.01	5.64	8.54	10.64	21.20	29.08	22.34	36.82	29.92	20.06	25.01	14.20	14.54
DALYs	42.64	190.72	1023.72	440.62	143.83	245.95	752.54	2468.12	3462.24	2294.96	5375.57	4949.34	2857.80	5603.17	4228.25	6377.87
Severe Dengue																
YLLs	72.33	510.41	1821.95	746.35	312.11	656.35	1267.79	3425.01	6612,57	3724.61	6813.32	5577.22	3570.18	5869.40	3667.12	4154.25
YDLs	0.02	0.31	2.45	1.47	0.30	0.51	1.32	4.97	12.62	5.66	11.12	7.27	2.77	2.87	1.92	1.71
DALYs	72.35	510.72	1824.40	747.82	312.41	656.86	1269.11	3429.98	6625.18	3730.27	6824.45	5584.49	3572.95	5872.27	3669.04	4155.96

Note: YLL: Years of Life Lost; YDL: Years Lost due to Disability; DALY: Disability-Adjusted Life Years

4. Discussion

We believe our study is the first study that has comprehensively evaluated the economic and health burden of dengue in an endemic country from a public health perspective, accounting for all dengue and severe dengue in Brazil from 2000 to 2015. This is different from previous publications that were conducted involving only some regions of Brazil [33, 38], utilized interviews [34, 55, 56], one city [57] and in some regions of a South American country [34, 58]. Marteli and collaborators (2015) also estimated the economic burden of dengue in Brazil ranging from USD 371 million (2009) to USD 1228 million (2013). However, the authors used the dengue notification registers from SINAN (Sep/2012 to Oct/2013) to estimate the burden [33] and not just the SUS costs, and their analysis was only based on 6 cities. As a result, there is likely to be an appreciable over-estimation of the actual costs from a public healthcare (SUS) perspective. This was the case. In our study, between 2000 and 2015, there were a total of 9,599,678 (dengue: 98%; severe dengue: 2%) and 739,177 hospitalization cases (dengue: 95.9%; severe dengue: 4.1%) generating a total cost of USD159.5 million dengue and USD10.2 million for severe dengue through SUS services during the study period. Our findings are similar to a study conducted in the Philippines for dengue in terms of the profile of dengue and its impact on hospitalization [59].

Our study demonstrated a median incidence of dengue and severe dengue of 273 and 3 cases per 100,000 inhabitants, respectively, and a low hospitalization incidence of 25 (dengue) and 1 (severe dengue) case per 100,000 inhabitants between 2000 and 2015. The high number of cases documented in the national databases in 2002, 2008, 2010, 2013 and 2015, reflect the epidemics registered in these years in Brazil [17,18]. Regarding the profile of dengue cases, of the 9,599,678 [17] cases notified for this infection in Brazil between 2000 and 2015, only 7.7% (739,177) used SUS services. This confirms previous studies that the majority of dengue patients self-treat at home and did not receive ambulatory care or hospitalization services. This may well explain the relatively low observed costs over the 16 years despite high prevalence rates compared for instance with the study of Marteli et al [33]. In addition, the number of recorded dengue cases may be an under-estimate if the vast majority of patients are self-treated despite compulsory notification. However, using real world data involving hospitalization services within SUS (epidemiology and cost), together with other economic analysis [60, 61], appreciably contributes to discussions involving the possible incorporation of any new dengue vaccine into the Brazilian National Immunization Program at requested prices alongside other measures to control the virus and its symptoms.

Our study demonstrated considerable variation in cases, with high occurrence of dengue in the Northeast and Southeast regions of Brazil, similar to the findings of Teixeira and collaborators [36]. This is also similar to the findings of the National Survey by Household in 2013 whereby the Southeast (18.2%) and Northeast (48.0%) regions contributed most of the dengue cases in Brazil [44, 62]. The southeast region is the most populated region in the country [44, 62], and the accelerated and disorganized urbanization in some States helps to understand the burden of dengue in these areas [63, 64]. In the Northeast region, the lack of adequate sanitation is more frequent compared with the Southeast, which could also help explain the higher prevalence there [62].

With respect to calculating the economic burden of dengue, encouragingly, our study was able to capture all dengue services in SUS Databases across the country, adding robustness to our findings. Recent publications have applied an expansion factor where all municipalities have not been incorporated into the analysis. In the Philippines, the authors adjusted the reported number of clinically diagnosed dengue cases using an expansion factor of 7.0 and estimated an annual average of 842,867 cases with direct medical costs (in 2012 US dollars) of USD 345 million during 2008-2012 [59]. They estimated the aggregate direct medical cost considering a scenario where all clinical cases consumed public financial resources. In our study, typically SUS only spent financial resources on patients who had severe symptoms rather than milder cases, with these self-paid. This aspect could have influenced the higher costs in the Philippines compared to our findings.

Shepard et al (2014) conducted an economic and epidemiological study in India between 2006 and 2012, which projected 5,778,406 annual dengue cases in the country (national expansion factor: 282). They calculated that the direct medical costs were USD 548 million per annum with this infection considering the number of cases adjusted with the expansion factor, different again to our study [59].

The aggregate cost of hospitalization associated with dengue compared to ambulatory care costs were higher in Cambodia [30] and India [37], similar to our results.

Regarding the morbidity associated with dengue, in Mexico, dengue hospitalization cases represented only 29.2 (2010) and 27.2 (2011) DALYs. This compares with our findings of 3372 to 6496 since 2007 (Table 5). This is similar though to other studies evaluating DALYs in Brazil [38]. However, other countries such as Cambodia had a higher burden of dengue in 2006 at 5,603 DALYs and 2007 at 16,330 DALYs [30]. This shows the value at looking at metrics such as DALYs when developing public health policies.

Along with considering funding new technologies to treat dengue, it is important to highlight the costs the Brazilian government already invests every year to help prevent dengue, chikungunya and zika virus, which are associated with the same vector [65, 66]. These costs would continue even with increasing eradication of dengue with effective vaccination and other programs. In 2014, the Brazilian government authorized the transfer of the Health Surveillance Component of R$150.0 million BRL (US$ 45.05 million), which corresponds to 12% of the annual fixed health surveillance budget, for activities to prevent and control the arboviruses [67]. Potential prices paid for such a vaccine also have to be evaluated against patients' willingness to pay for such a vaccine [60]. In addition, from the National Dengue Profile obtained via SUS databases, we did not find any register associating the seroprevalence with each one of the procedures registered (ambulatory and hospitalization). Considering that the first dengue vaccine approved in the country (Dengvaxia®) has a different efficacy for each serotype [28], it could be important to evaluate the dengue seroprevalence in the country. In this context, it is important to develop a National Seroprevalence Study for dengue to better inform future policy decision making if this does not already exist.

We acknowledge that there are limitations with our study. We did not include costs such as costs per night and cost per inpatient stay, because they were not available in the SUS databases. However, all available clinical procedures (registers and costs) associated with dengue and severe dengue treatment within SUS were included in our calculations. We also did not include ambulatory care costs and costs associated with patients who typically manage their condition at home as this data is not captured within the available SUS datasets. As a result, the direct medical costs reported by us are likely to be an under-estimate. We also did not consider the sub-notification cases as our principal objective was to estimate the costs involved with the registers for dengue in the country according to the SUS databases (SIA/SIH/SUS). Another limitation of this study involved the absence of the economic assessment of the dengue notification scenario. Additionally in our study, we did not include indirect costs as we adopted the perspective of SUS. We are aware other studies have demonstrated the important contribution of these costs for dengue [29, 38, 55, 57, 58].

We also used the discount rate of the of the Brazilian Ministry of Health to calculate the burden of the infection [39, 40] which is different from that applied in Global Burden of Disease (GDB) [52]. Despite these limitations, we believe that we have provided reliable data for SUS based on the direct medical costs under its jurisdiction and the current epidemiological impact of dengue in Brazil.

5. Conclusion

Our study demonstrated the high costs and epidemiological context in Brazil from the SUS perspective associated with dengue over the past 16 years from 2000 to 2015. The challenge to eliminate the arboviruses in Brazil needs to continue and there needs to be investment and implementation of a national program with continuous and rigorous monitoring of the presence of the vector in all municipalities throughout Brazil and not only some cities. If the country had success in the past to eradicate this vector, it would be important to implement and invest efforts to conduct activities and repeat the satisfactory result of eradicating *Aedes aegypti*.

The potential incorporation of any vaccine for dengue needs to be carefully examined within the Brazilian context as prevention programmes are ongoing and there are also considerable demands on available resources. In this context, and given the current economic situation, there is an urgent need for a robust cost-effectiveness analysis of any new dengue vaccine or treatment of the infection to guide future purchasing decisions. These are considerations for the future.

6. Key Issues

- A total of 702,270 and 29,925 individuals utilized SUS services to treat, respectively, dengue and severe dengue in Brazil, totalizing 739,177 hospitalizations and 4986 deaths associated with this infection in the country, between January 2000 and December 2015. This resulted in almost USD159 million and USD10 million spent by SUS to treat dengue and severe dengue, respectively, between January 2000 and December 2015.
- Annual DALYs estimates ranging between 42.64 to 6,824.45 over the study period associated with DENV in Brazil.
- The use of real world numbers involving the hospitalization services within the Brazilian public health system (epidemiology and cost) combined with other economic analysis can contribute to discussions involving the possible incorporation of a dengue vaccine into the Brazilian National Immunization Program.
- The Brazilian government urgently needs to proactively evaluate the real costs and clinical benefits of any potential dengue vaccination program by the National Immunization Program to guide future decision making.

Author contributions

IG wrote the first draft; IG, LS, AS, IM and AM helped undertake the study and the analysis; IG, AM, SM, BG, MB and AGJ subsequently revised the draft and produced the final manuscript. All authors approved the final manuscript.

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Declaration of interest

The authors declare that there are no conflicts of interest.

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